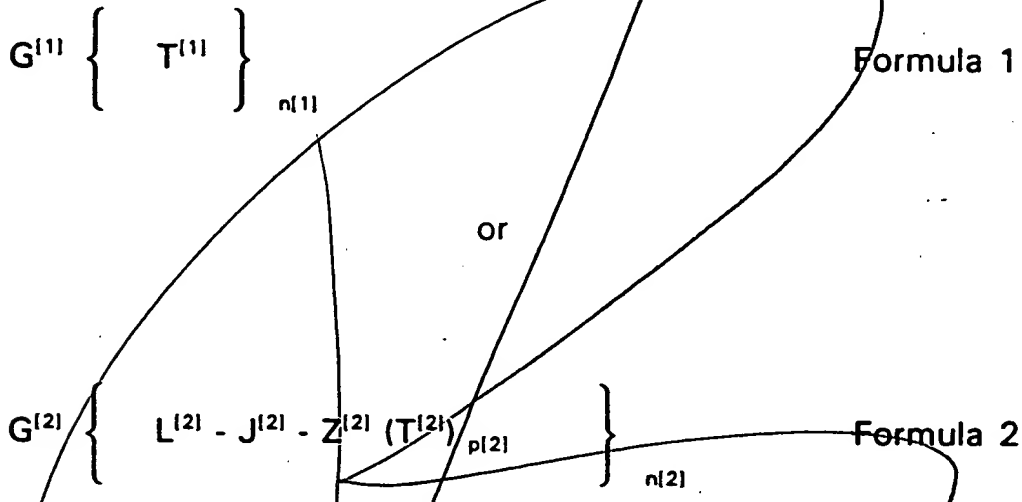
Claims

WE CLAIM:

1. A conjugate comprising (a) biological or chemical molecules reacted with (b) a chemically-defined, non-polymeric valency platform molecule of the formula:



Formula 1

or

Formula 2

wherein

each of $G^{[1]}$ and $G^{[2]}$, if present, is independently a linear, branched or multiply-branched chain comprising 1-2000 chain atoms selected from the group C, N, O, Si, P and S;

each of the $n^{[1]}$ moieties shown as $T^{[1]}$ and each of the $p^{[2]} \times n^{[2]}$ moieties shown as $T^{[2]}$ is independently chosen from the group NHR^{SUB} (amine), $C(=O)NHNHR^{SUB}$ (hydrazide), $NHNHR^{SUB}$ (hydrazine), $C(=O)OH$ (carboxylic acid), $C(=O)OR^{ESTER}$ (activated ester), $C(=O)OC(=O)R^{B}$ (anhydride), $C(=O)X$ (acid halide), $S(=O)_2X$ (sulfonyl halide), $C(=NR^{SUB})OR^{SUB}$ (imidate ester), NCO (isocyanate), NCS (isothiocyanate), $OC(=O)X$ (haloformate), $C(=O)OC(=NR^{SUB})NHR^{SUB}$ (carbodiimide adduct), C(=O)H

(aldehyde), $C(=O)R^B$ (ketone), SH (sulfhydryl or thiol), OH (alcohol), $C(=O)CH_2X$ (haloacetyl), $R^{ALK}X$ (alkyl halide), $S(=O)_2OR^{ALK}X$ (alkyl sulfonate), NR^1R^2 wherein R^1R^2 is $-C(=O)CH=CHC(=O)-$ (maleimide), $C(=O)CR^B=CR^B_2$ (α,β-unsaturated carbonyl), R^{ALK}-Hg-X (alkyl mercurial), and $S(=O)CR^B=CR^B_2$ (α,β-unsaturated sulfone);

wherein

each X is independently a halogen of atomic number greater than 16 and less than 54 or other good leaving group;

each R^{ALK} is independently a linear, branched, or cyclic alkyl (1-20C) group;

each R^{SUB} is independently H, linear, branched, or cyclic alkyl (1-20C), aryl (6-20C), or alkaryl (7-30C);

each R^{ESTER} is independently N-hydroxysuccinimidyl, p-nitrophenoxy, pentafluorophenoxy, or other activating group;

each R^B is independently a radical comprising 1-50 atoms selected from the group C, H, N, O, Si, P and S;

each of the $n^{[2]}$ moieties shown as $L^{[2]}$, if present, is independently chosen from the group O, NR^{SUB} and S;

each of the $n^{[2]}$ moieties shown as $J^{[2]}$, if present, is independently chosen from the group C(=O) and C(=S);

$n^{[1]}$ = 1 to 32;

$n^{[2]}$ = 1 to 32;

$p^{[2]}$ = 1 to 8;

with the proviso that the product $n^{[2]} \times p^{[2]}$ be greater than 1 and less than 33;

each of the $n^{[2]}$ moieties shown as $Z^{[2]}$ is independently a radical comprising 1-200 atoms selected from the group C, H, N, O, Si, P and S, containing

attachment sites for at least p[illegible] functional groups on alkyl, alkenyl, or aromatic carbon atoms.

2. A conjugate according to claim 1, wherein the biological molecules comprise polynucleotide duplexes of at least about 20 base pairs each bound to the valency platform molecule, the duplexes each having a significant binding activity for human systemic lupus erythematosus anti-dsDNA autoantibodies.

3. A conjugate according to claim 1, wherein the biological or chemical molecules are selected from the group consisting of carbohydrates, lipid, lipopolysaccharides, peptides, proteins, glycoproteins, single-stranded or double-stranded oligonucleotides, haptens, or chemical analogs thereof such as mimotopes, aptamers.

4. A conjugate according to claim 1, wherein the biological or chemical molecules are analogs of immunogens wherein (a) the analog binds specifically to B cells to which the immunogen binds specifically and (b) the conjugate lacks a T cell epitope.

5. The conjugate of claim 1, wherein the valency platform molecule is derivatized by a reagent selected from the group consisting of DABA, BAHA, $BAHA_{ox}$, and AHAB.

6. The conjugate of claim 2, wherein a linker molecule couples the duplexes to the valency platform molecule.

7. The conjugate of claim 6, wherein the linker molecule is selected from the group consisting of HAD and HAD_pS.

8. The conjugate of claim 2, wherein the duplexes are substantially homogeneous in length.

9. The conjugate of claim 2, wherein the duplexes are substantially homogeneous in nucleotide composition.

10. The conjugate of claim 2, wherein the duplexes are 20 to 50 bp in length.

11. The conjugate of claim 2, wherein the duplexes are bound to the valency platform molecule at or proximate one of their ends.

12. The conjugate of claim 2, wherein the conjugate is a tolerogen for human systemic lupus erythematosus.

13. A conjugate according to claim 2, wherein the polynucleotide duplexes have a B-DNA type helical structure and a significant binding activity for human systemic lupus erythematosus anti-dsDNA autoantibodies.

14. A pharmaceutical composition for treating lupus comprising the conjugate of claim 2 formulated with a pharmaceutically acceptable injectable vehicle.

15. A method for treating an individual for lupus comprising administering a therapeutically effective amount of the composition claim 14 to an individual in need of such treatment.

16. A method for making the conjugate of claim 2, comprising:

(a) bonding a multiplicity of single-stranded polynucleotides of at least about 20 base pairs each on the valency platform molecule; and

(b) annealing complementary single-stranded polynucleotides to the single-stranded polynucleotides conjugated to the valency platform molecule to form said duplexes.

17. A pharmaceutical composition for treating an antibody-mediated pathology comprising a therapeutically effective amount of the conjugate of claim 2, combined with a pharmaceutically acceptable carrier.

18. A method of inducing specific B cell anergy to an immunogen in an individual comprising administering to the individual an effective amount of the conjugate of claim 17.

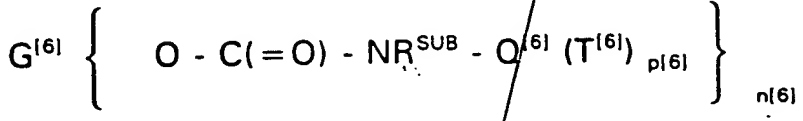
19. A method of treating an individual for an antibody-mediated pathology in which undesired antibodies are produced in response to an immunogen comprising administering a therapeutically effective amount of the conjugate of claim 17 to the individual.

20. A method for making a conjugate according to claim 2, comprising

(a) covalently bonding the analog of the immunogen lacking T cell epitopes to the chemically-defined valency platform molecule to form a conjugate; and

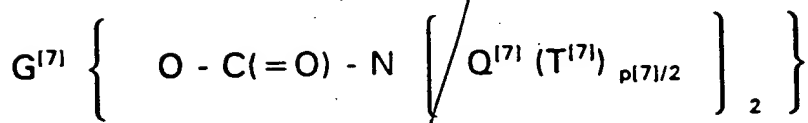
(b) recovering the conjugate from the reaction mixture.

21. A chemically-defined, non-polymeric valency platform molecule of the formula:



Formula 6

or



Formula 7

wherein

each of $G^{[6]}$ and $G^{[7]}$, if present, is independently a linear, branched or multiply-branched chain comprising 1-2000 chain atoms selected from the group C, N, O, Si, P and S;

each of the $n^{[6]} \times p^{[6]}$ moieties shown as $T^{[6]}$ and each of the $n^{[7]} \times p^{[7]}$ moieties shown as $T^{[7]}$ is independently chosen from the group NHR^{SUB} (amine), $C(=O)NHNHR^{SUB}$ (hydrazide), $NHNHR^{SUB}$ (hydrazine), $C(=O)OH$ (carboxylic acid), $C(=O)OR^{ESTER}$ (activated ester), $C(=O)OC(=O)R^{B}$ (anhydride), $C(=O)X$ (acid halide), $S(=O)_2X$ (sulfonyl halide), $C(=NR^{SUB})OR^{SUB}$ (imidate ester), NCO (isocyanate), NCS (isothiocyanate), $OC(=O)X$ (haloformate), $C(=O)OC(=NR^{SUB})NHR^{SUB}$ (carbodiimide adduct), $C(=O)H$ (aldehyde), $C(=O)R^{B}$ (ketone), SH (sulfhydryl or thiol), OH (alcohol), $C(=O)CH_2X$ (haloacetyl), $R^{ALK}X$ (alkyl halide), $S(=O)_2OR^{ALK}X$ (alkyl sulfonate), NR^1R^2 wherein R^1R^2 is $-C(=O)CH=CHC(=O)-$ (maleimide), $C(=O)CR^{B}=CR^{B}_2$ (α,β-unsaturated carbonyl),

R^{ALK}-Hg-X (alkyl mercurial), and $S(=O)CR^B=CR^B_2$ (α,β-unsaturated sulfone);

wherein

each X is independently a halogen of atomic number greater than 16 and less than 54 or other good leaving group;

each R^{ALK} is independently a linear, branched, or cyclic alkyl (1-20C) group;

each R^{SUB} is independently H, linear, branched, or cyclic alkyl (1-20C), aryl (1-20C), or alkaryl (1-30C);

each R^{ESTER} is independently N-hydroxysuccinimidyl, p-nitrophenoxy, pentafluorophenoxy, or other activating group;

each R^B is independently a radical comprising 1-50 atoms selected from the group C, H, N, O, Si, P and S;

$n^{[6]}$ = 1 to 32;

$p^{[6]}$ = 1 to 8;

with the proviso that the product $n^{[6]} \times p^{[6]}$ be greater than 1 and less than 33;

$n^{[7]}$ = 1 to 32;

$p^{[7]}$ = 2, 4, 6 or 8;

with the proviso that the product $n^{[7]} \times p^{[7]}$ be greater than 1 and less than 33;

each of the $n^{[6]}$ moieties shown as $Q^{[6]}$ and each of the $2 \times n^{[7]}$ moieties shown as $Q^{[7]}$ is independently a radical comprising 1-100 atoms selected from the group C, H, N, O, Si, P and S, containing attachment sites for at least $p^{[6]}$ (for $Q^{[6]}$) or $p^{[7]}/2$ (for $Q^{[7]}$, where $p^{[7]}/2$ is an integer) functional groups on alkyl, alkenyl, or aromatic carbon atoms.